Claim 16, lines 1-2, change "is adapted to be applied" to --has an adhesive for attachment--.

Claim 17, lines 1-2, change "is adapted to be applied" to --has an adhesive for attachment--.

Please cancel claim 18 without prejudice or disclaimer.

REMARKS

By the present Amendment, minor revisions have been made in the specification. In addition, independent claims 1 and 10 have been amended to define the invention with greater particularity, claims 16 and 17 have been amended to provide a further structural limitation and claim 18 has been cancelled without prejudice or disclaimer. The new claims are believed to clearly and distinctly define the various aspects of the present invention in full compliance with the provisions of the second paragraph of 35 U.S.C. §112 and in a manner which is patentable over the cited prior art.

As explained in greater detail in the specification, the presently claimed invention relates to a method of delivering an analgesic drug selected from the group consisting of fentanyl salts and sufentanil salts through a body surface by electrotransport from an electrotransport delivery device having a donor reservoir containing an at least partially aqueous solution of a fentanyl salt or a sufentanil salt. As is known in the art, fentanyl and sufentanil are extremely potent analgesic drugs (fentanyl being approximately 100

times more potent than morphine and sufentanil being even more potent) whose administration to a patient must be carefully controlled. With passive transdermal patches, the analgesic drug was continuously delivered to the patient with the amount of drug in the patch being determined by the dosage to be administered. One of the drawbacks of passive transdermal patches is that there is a significant lag time required to achieve peak plasma levels. While electrotransport delivery devices can significantly reduce the lag time necessary to achieve peak plasma levels, it has been difficult to maintain a predictable transdermal electrotransport flux at a particular applied current level.

The present invention addresses the significant challenge in the art and enables an essentially constant electrotransport flux to be obtained at an applied electrotransport current level. In particular, it has been found that by maintaining the concentration of a fentanyl salt in an aqueous solution in the donor reservoir at a level above about 11 mM or by maintaining the concentration above about 1.7 mM when the drug is a sufentanil salt, the electrotransport flux can be maintained at an essentially constant level substantially throughout the analgesic drug electrotransport delivery period wherein the analgesic drug is delivered through the body surface. In this respect, it is important to understand that the defined relatively high concentration of fentanyl salt or sufentanil salt is maintained during the delivery period and that accordingly, delivery is terminated before the contents of the reservoir are depleted. By thus following the present invention, one can achieve a high level of predictability since the delivery of the drug is terminated before a significant decrease in the normalized flux occurs.

The invention as defined in the claims now of record are neither anticipated nor rendered obvious by any of the cited prior art. In particular, Phipps et al, U.S. Patent No. 5,423,739, relates to a device and method for iontophoretic drug delivery. As the Examiner has noted, the device can include a reservoir with little or no water and a medicament. While fentanyl and sufentanil are identified as possible active agents, they are but two materials in a lengthy list that extends over columns 13 and 14 of the patent and neither of these materials are included in the patent examples.

The '739 patent also does not disclose the claimed concentration levels (which are significantly higher than what one might consider for these potent drugs) and hence cannot anticipate any of the claims now of record. Moreover, the patent does not teach the claimed concentration levels of fentanyl salt or sufentanil salt are to be maintained substantially throughout the analgesic drug electrotransport delivery period wherein the analgesic is delivered through the body surface in order to avoid a substantial decrease in normalized flux. Even considering the embodiment where the reservoir contains little or no water, it is not the concentration of the drugs during water addition that is being claimed, but rather the concentration during the period of electrotransport delivery. Furthermore, the '739 patent does not recognize the importance of maintaining the concentration of the salt at the defined levels substantially throughout the analgesic drug transport delivery period so that drug delivery is terminated before the contents of the reservoir are exhausted. Indeed, it would be counter-intuitive to terminate drug delivery while the concentration of fentanyl and sufentanil salts are substantially at the defined levels. Hence, the '739 patent falls short from being sufficient to in any way anticipate or render obvious any of the claims now of record.

The Examiner's further reliance on Phipps et al, U.S. Patent No. 5,125,894, does not remedy any of the deficiencies of the '739 patent. The '894 patent has been primarily relied on to show the effect of concentration of drug ions on the rate of drug delivery at constant current as set forth at column 11, lines 8-16. While the stated general effect is known, those skilled in the art would not be led to the specific levels defined in the claims and would certainly not be led to maintaining the defined levels of fentanyl salt of sufentanil salt (which are again higher than what one would believe appropriate for such potent drugs) substantially throughout the analgesic drug electrotransport delivery period wherein the analgesic drug is delivered through the body surface. Thus, since the '894 patent likewise does not embody or specifically teach the claimed high concentration levels of the defined fentanyl and sufentanil salts, the combination of the '739 and '894 patents also would not lead to the presently claimed invention.

The Examiner's additional reliance on the combination of Weaver et al, U.S. Patent No. 5,019,034, Sibalis et al, U.S. Patent No. 4,878,892, and Levy et al, U.S. Patent No. 4,822,802, is believed to be improperly based on the teachings of applicant's own specification. In particular, neither Weaver et al nor Sibalis et al in any way relate to the electrotransport of fentanyl salt of sufentanil salt. Indeed, Sibalis et al specifically relates to the electrolytic transdermal delivery of polypeptides which the patent itself distinguishes from the delivery of other materials in the passage at column 1, lines 26-50. On the other hand, Levy et al does describe the transdermal administration of fentanyl and sufentanil, but relates to a passive transdermal system which is significantly different from electrotransport systems.

Even if there existed some proper basis for combining the disparate teachings of the respective patents, one would still not obtain the presently claimed invention. In this respect, the Examiner's statement on page 5 of the Official Action that "it is considered obvious to deliver fentanyl and sufentanil by electroporation/electroosmosis in various medicament concentrations..." misinterprets the invention. That is, the invention does not reside in delivering fentanyl or sufentanil at a particular concentration. Instead, the invention entails maintaining the concentration of the salts in the reservoir at the defined high levels in order to obtain a predictable transdermal electrotransport flux at any particularly applied electrotransport current level. Thus, it is apparent that if one correctly interprets the claims, this hypothetical combination of prior art posed by the Examiner in the Action also falls far short of being sufficient to reject any of the claims of record.

For the reasons provided above, applicant respectfully submits that the claims now of record fully comply with the provisions of 35 U.S.C. § 112 and are patentable over the cited prior art. Accordingly, reconsideration and allowance of the present application are requested.

Respectfully submitted,

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